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NEWS 2	JAN 12	Match STN Content and Features to Your Information Needs, Quickly and Conveniently
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NEWS 4	FEB 16	STN Express Maintenance Release, Version 8.4.2, Is Now Available for Download
NEWS 5	FEB 16	Derwent World Patents Index (DWPI) Revises Indexing of Author Abstracts
NEWS 6	FEB 16	New FASTA Display Formats Added to USGENE and PCTGEN
NEWS 7	FEB 16	INPADOCDB and INPAFAMDB Enriched with New Content and Features
NEWS 8	FEB 16	INSPEC Adding Its Own IPC codes and Author's E-mail Addresses
NEWS 9	APR 02	CAS Registry Number Crossover Limits Increased to 500,000 in Key STN Databases
NEWS 10	APR 02	PATDPAFULL: Application and priority number formats enhanced
NEWS 11	APR 02	DWPI: New display format ALLSTR available
NEWS 12	APR 02	New Thesaurus Added to Derwent Databases for Smooth Sailing through U.S. Patent Codes
NEWS 13	APR 02	EMBASE Adds Unique Records from MEDLINE, Expanding Coverage back to 1948
NEWS 14	APR 07	CA/CAplus CLASS Display Streamlined with Removal of Pre-IPC 8 Data Fields
NEWS 15	APR 07	50,000 World Traditional Medicine (WTM) Patents Now Available in CAplus
NEWS 16	APR 07	MEDLINE Coverage Is Extended Back to 1947
NEWS 17	JUN 16	WPI First View (File WPIFV) will no longer be available after July 30, 2010
NEWS 18	JUN 18	DWPI: New coverage - French Granted Patents
NEWS 19	JUN 18	CAS and FIZ Karlsruhe announce plans for a new STN platform
NEWS 20	JUN 18	IPC codes have been added to the INSPEC backfile (1969-2009)
NEWS 21	JUN 21	Removal of Pre-IPC 8 data fields streamline displays in CA/CAplus, CASREACT,and MARPAT
NEWS 22	JUN 21	Access an additional 1.8 million records exclusively enhanced with 1.9 million CAS Registry Numbers -- EMBASE Classic on STN
NEWS 23	JUN 28	Introducing "CAS Chemistry Research Report": 40 Years of Biofuel Research Reveal China Now Atop U.S. in Patenting and Commercialization of Bioethanol

NEWS EXPRESS FEBRUARY 15 10 CURRENT WINDOWS VERSION IS V8.4.2,
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FILE 'HOME' ENTERED AT 12:39:43 ON 28 JUN 2010

=> file registry
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                      0.22       0.22

FILE 'REGISTRY' ENTERED AT 12:39:57 ON 28 JUN 2010
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STRUCTURE FILE UPDATES:   27 JUN 2010  HIGHEST RN 1228427-89-1
DICTIONARY FILE UPDATES:  27 JUN 2010  HIGHEST RN 1228427-89-1

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TSCA INFORMATION NOW CURRENT THROUGH January 8, 2010.

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predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> s carboxypeptidase G2
          3250 CARBOXYPEPTIDASE
          8231 G2
L1          44 CARBOXYPEPTIDASE G2
                (CARBOXYPEPTIDASE(W)G2)

=> s methotrexate
L2         120 METHOTREXATE

=> s raltitrexed
L3           1 RALTITREXED

=> s AG 2037
        106947 AG
           155 AGS
```

```
        107095 AG
                 (AG OR AGS)
          2617 2037
L4           1 AG 2037
                 (AG(W)2037)

=> s LY 309887
         15847 LY
             1 LIES
         15848 LY
                 (LY OR LIES)
             7 309887
L5           1 LY 309887
                 (LY(W)309887)

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               44.98      45.20

FILE 'CAPLUS' ENTERED AT 12:40:57 ON 28 JUN 2010
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FILE COVERS 1907 - 28 Jun 2010  VOL 153 ISS 1
FILE LAST UPDATED: 27 Jun 2010  (20100627/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Apr 2010
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Apr 2010

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2010.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l1
L6           29 L1

=> s l6 and (l2 or l3 or l4 or l5)
         18420 L2
           856 L3
            16 L4
            35 L5
L7           0 L6 AND (L2 OR L3 OR L4 OR L5)

=> E US2007-590789/ap
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E1            1     US2007-590784/AP
E2            1     US2007-590786/AP
E3            1 --> US2007-590789/AP
E4            1     US2007-590790/AP
E5            1     US2007-5908/AP
E6            1     US2007-590801/AP
E7            1     US2007-590802/AP
E8            1     US2007-590808/AP
E9            1     US2007-590812/AP
E10           1     US2007-590813/AP
E11           1     US2007-590816/AP
E12           1     US2007-590817/AP

=> s e3
L8            1 US2007-590789/AP

=> d l8 ibib ind

L8   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER:         2005:1004581  CAPLUS
DOCUMENT NUMBER:          143:299139
TITLE:                    Use of enzyme carboxypeptidase G for combating
                          toxicity caused by an antifolate compound
INVENTOR(S):              Melton, Roger; Atkinson, Anthony
PATENT ASSIGNEE(S):       Protherics Molecular Design Limited, UK
SOURCE:                   PCT Int. Appl., 54 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.            KIND   DATE        APPLICATION NO.          DATE
     ---------------       ----   --------    -------------------      --------
     WO 2005084695          A2    20050915    WO 2005-GB751            20050228
     WO 2005084695          A3    20051208
          W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
              CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
              GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
              LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
              NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM,
              SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
          RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
              AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
              EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
              RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
              MR, NE, SN, TD, TG
     AU 2005218987          A1    20050915    AU 2005-218987           20050228
     CA 2557610             A1    20050915    CA 2005-2557610          20050228
     EP 1727548             A2    20061206    EP 2005-717830           20050228
          R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
              IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR
     CN 1950088             A     20070418    CN 2005-80013842         20050228
     BR 2005008053          A     20070717    BR 2005-8053             20050228
     JP 2007524711          T     20070830    JP 2007-500299           20050228
     ZA 2006007171          A     20071128    ZA 2006-7171             20050228
     MX 2006009711          A     20070516    MX 2006-9711             20060825
     KR 2007036023          A     20070402    KR 2006-717341           20060828
     IN 2006DN04935         A     20070817    IN 2006-DN4935           20060828
     US 20070243182         A1    20071018    US 2007-590789           20070212 <--
PRIORITY APPLN. INFO.:                         GB 2004-4487        A    20040228
                                               WO 2005-GB751       W    20050228
```

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 143:299139
IPCI A61K0038-16 [ICM,7]; A61K0031-517 [ICS,7]; A61K0031-519 [ICS,7]; A61K0038-48 [ICS,7]; A61K0038-43 [ICS,7,C*]; A61P0035-00 [ICS,7]
IPCR A61K0031-517 [I,C*]; A61K0031-517 [I,A]; A61K0031-519 [I,C*]; A61K0031-519 [I,A]; A61K0038-43 [I,C*]; A61K0038-48 [I,A]
CC 1-12 (Pharmacology)
Section cross-reference(s): 7
ST carboxypeptidase G antifolate toxicity treatment
IT Antirheumatic agents
Antitumor agents
(antifolates as; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Bone marrow
Liver
(antifolates toxicity to; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Carcinoma
Liver, neoplasm
Mammary gland, neoplasm
Multiple sclerosis
Neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Prostate gland, neoplasm
Psoriasis
Rheumatoid arthritis
Stomach, neoplasm
(antifolates treatment of; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Disease, animal
(asthenia, from antifolate toxicity; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Intestine, neoplasm
(colon, antifolates treatment of; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Mucous membrane
(disease, inflammation, from antifolate toxicity; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Platelet (blood)
(disease, thrombocytopenia, from antifolate toxicity; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Pregnancy disorders
(ectopic pregnancy, antifolates treatment of; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Metabolic pathways
(folate pathway, rescue agents for; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Anemia (disease)
Anorexia
Dehydration, physiological
Diarrhea
Fatigue, biological

Fever and Hyperthermia
Leukocytopenia
Nausea
Vomiting
(from antifolate toxicity; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Hepatotoxicity
Myelotoxicity
(from antifolates; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Transplant and Transplantation
(graft-vs.-host reaction, antifolates treatment of; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Mesothelium, neoplasm
(mesothelioma, antifolates treatment of; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Inflammation
(mucous membrane, from antifolate toxicity; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Agranulocytosis
(neutropenia, from antifolate toxicity; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Lung, neoplasm
(non-small-cell carcinoma, antifolates treatment of; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Carcinoma
(pulmonary non-small-cell, antifolates treatment of; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Skin, disease
(rash, from antifolate toxicity; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Intestine, neoplasm
(rectum, antifolates treatment of; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Neoplasm
(solid, antifolates treatment of; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Inflammation
Mouth, disease
(stomatitis, from antifolate toxicity; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Blood, disease
(thrombocytopenia, from antifolate toxicity; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)
IT Combination chemotherapy
Drug toxicity
Enzyme kinetics
Human
Michaelis constant

(use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)

IT 9002-03-3, Dihydrofolate reductase 9031-61-2, Thymidylate synthase 9032-02-4
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antifolates inhibition of; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)

IT 50-89-5, Thymidine, biological studies 1492-18-8, Leucovorin calcium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(folate pathway rescue agent; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)

IT 635-65-4, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hyperbilirubinemia, from antifolate toxicity; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)

IT 59-30-3, Folic acid, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)

IT 864475-16-1
RL: PRP (Properties)
(unclaimed sequence; use of enzyme carboxypeptidase G for combating toxicity caused by an antifolate compound)

IT 112887-68-0, Tomudex 127228-54-0, LY309887 177575-17-6, AG2034 446022-33-9, AG2037
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)

IT 384438-26-0, GenBank M12599
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)

IT 9074-87-7, Carboxypeptidase G
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of enzyme carboxypeptidase G for combating toxicity of antifolate compds. by deglutamylation combined with folate pathway rescue)

=> file zcaplus

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FILE COVERS 1907 - 28 Jun 2010 VOL 153 ISS 1
FILE LAST UPDATED: 27 Jun 2010 (20100627/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2010
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Apr 2010

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```
=> set exp continuous
SET COMMAND COMPLETED

=> e carboxypeptidase g/ct
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E13          0     16      CARBOXYPEPTIDASE D/CT
E14          0     14      CARBOXYPEPTIDASE E/CT
E15          0        --> CARBOXYPEPTIDASE G/CT
E16          0      2      CARBOXYPEPTIDASE G2/CT
E17          0      2      CARBOXYPEPTIDASE H/CT
E18          0      2      CARBOXYPEPTIDASE I/CT
E19          0      2      CARBOXYPEPTIDASE II (CPW)/CT
E20          0      2      CARBOXYPEPTIDASE KEX1/CT
E21          0     10      CARBOXYPEPTIDASE M/CT
E22          0     22      CARBOXYPEPTIDASE N/CT
E23          0      2      CARBOXYPEPTIDASE N1/CT
E24          0      3      CARBOXYPEPTIDASE R/CT

=> e carboxypeptidase g2/ct
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E25          0     16      CARBOXYPEPTIDASE D/CT
E26          0     14      CARBOXYPEPTIDASE E/CT
E27          0      2 --> CARBOXYPEPTIDASE G2/CT
E28          0      2      CARBOXYPEPTIDASE H/CT
E29          0      2      CARBOXYPEPTIDASE I/CT
E30          0      2      CARBOXYPEPTIDASE II (CPW)/CT
E31          0      2      CARBOXYPEPTIDASE KEX1/CT
E32          0     10      CARBOXYPEPTIDASE M/CT
E33          0     22      CARBOXYPEPTIDASE N/CT
E34          0      2      CARBOXYPEPTIDASE N1/CT
E35          0      3      CARBOXYPEPTIDASE R/CT
E36          0      2      CARBOXYPEPTIDASE RISC/CT

=> E e3+all
RELATIONSHIP 'ALL' IGNORED.
RELATIONSHIPS DO NOT EXIST FOR FIELD 'AP'.
E37          1      US2007-590784/AP
E38          1      US2007-590786/AP
E39          1 --> US2007-590789/AP
E40          1      US2007-590790/AP
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E41           1     US2007-5908/AP
E42           1     US2007-590801/AP
E43           1     US2007-590802/AP
E44           1     US2007-590808/AP
E45           1     US2007-590812/AP
E46           1     US2007-590813/AP
E47           1     US2007-590816/AP
E48           1     US2007-590817/AP

=> e e27+all
E49           0   -->  Carboxypeptidase G2/CT
E50           0     USE  Prostate specific membrane antigen/CT
********** END **********

=> file hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21      50.91

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FILE COVERS 1907 - 28 Jun 2010  VOL 153 ISS 1
FILE LAST UPDATED: 27 Jun 2010  (20100627/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Apr 2010
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Apr 2010

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s carboxypeptidase g2
         12396 CARBOXYPEPTIDASE
          1799 CARBOXYPEPTIDASES
         12916 CARBOXYPEPTIDASE
                 (CARBOXYPEPTIDASE OR CARBOXYPEPTIDASES)
         45095 G2
L9         224 CARBOXYPEPTIDASE G2
                 (CARBOXYPEPTIDASE(W)G2)

=> s l9 and (12 or 13 or 14 or 15)
         18420 L2
           856 L3
```

```
            16 L4
            35 L5
L10         35 L9 AND (L2 OR L3 OR L4 OR L5)

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          35 DUP REM L10 (0 DUPLICATES REMOVED)

=> d l11 1-35 ibib abs

L11  ANSWER 1 OF 35  HCAPLUS  COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER:        2009:1542257  HCAPLUS
TITLE:                   Glucarpidase following high-dose methotrexate: Update
                         on development
AUTHOR(S):               Patterson, Daniel M.; Lee, Siow-Ming
CORPORATE SOURCE:        Department of Oncology, UCL Cancer Institute,
                         University College Hospital, London, NW1 2PG, UK
SOURCE:                  Expert Opinion on Biological Therapy (2010), 10(1),
                         105-111
                         CODEN: EOBTA2; ISSN: 1471-2598
PUBLISHER:               Informa Healthcare
DOCUMENT TYPE:           Journal; General Review
LANGUAGE:                English
AB   Glucarpidase (Carboxypeptidase G2 or Voraxaze) is a
     recombinant enzyme that belongs to the class of carboxypeptidases which
     are naturally occurring enzymes.  Glucarpidase is able to cleave
     methotrexate (MTX) into non-cytotoxic metabolites that may help prevent or
     minimize subsequent toxicities such as renal failure.  In this review, the
     authors outline the discovery of the carboxypeptidase class of enzymes and
     the pre-clin. data demonstrating that glucarpidase is highly effective in
     the rapid reduction of MTX levels.  The authors summarize the compassionate
     use studies of glucarpidase for patients with nephrotoxicity following
     high dose MTX or with very high post-MTX levels and the current
     developmental status of the drug.  In conclusion, glucarpidase has been
     shown to be very useful in emergency situations following administration
     of high-dose MTX.  Glucarpidase has yet to receive marketing approval in
     the EU or USA, and we await further data from In conclusion, glucarpidase
     Phase I/II studies assessing routine prophylactic administration following
     high-dose methotrexate.
REFERENCE COUNT:         48    THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11  ANSWER 2 OF 35  HCAPLUS  COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER:        2009:285336  HCAPLUS
DOCUMENT NUMBER:         150:487273
TITLE:                   Metabolism-blocked antifolates as potential
                         anti-rheumatoid arthritis agents:
                         4-Amino-4-deoxy-5,8,10-trideazapteroyl-,-4'-
                         methyleneglutamic acid (CH-1504) and its analogs
AUTHOR(S):               McGuire, John J.; Haile, William H.
CORPORATE SOURCE:        Grace Cancer Drug Center, Roswell Park Cancer
                         Institute, Buffalo, NY, 14263, USA
SOURCE:                  Biochemical Pharmacology (2009), 77(7), 1161-1172
                         CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   4-Amino-4-deoxy-5,8,10-trideazapteroyl-,-4'-methyleneglutamic acid
     (CH-1504) is the prototype of a potentially therapeutically more selective
     class of antifolates for rheumatoid arthritis treatment.  This class is
     characterized by retention of dihydrofolate reductase (DHFR; EC 1.5.1.3)
     as their locus of action and transport by the reduced folate carrier (RFC;
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SLC19A1), but their lack of metabolism by known pathways of antifolate (e.g., methotrexate (MTX)) metabolism Five new CH-1504 analogs (CHL-001-CHL-005) were synthesized and diastereomers of CH-1504 itself were obtained by preparative chiral HPLC; all were characterized biochem. The analogs are not metabolized by aldehyde oxidase (EC 1.2.3.1), carboxypeptidase G2 (EC 3.4.17.11), or (excepting CHL-003) folylpolyglutamate synthetase (EC 6.3.2.17) and thus, unlike MTX, are "metabolism-blocked". All analogs are potent DHFR inhibitors; several are nearly as potent as MTX or CH-1504. Each analog uses the RFC for transport, although with varying apparent affinities. In contrast, each weakly inhibits other enzymes of folate metabolism relevant to rheumatoid arthritis therapy (thymidylate synthase (EC 2.1.1.45), two formyltransferases of purine biosynthesis (EC 2.1.2.2 and EC 2.1.2.3), and 5,10-methylenetetrahydrofolate reductase (EC 1.5.1.20)). Biochem. characterization showed one 4'-diastereomer of racemic CH-1504 was significantly more active than the other. Based on literature data concerning the effect of - and -glutamic acid substitution on antifolate activity, it is likely that the diastereomer containing -4'-methylene-glutamic acid is the more active. Because of concern about potential pharmacokinetic and biochem. effects of -4'-methylene-glutamic acid-containing species, these data suggest that future analogs should contain only -4'-methylene-glutamic acid. Overall, these data provide several interesting new leads for preclin. development.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:103326 HCAPLUS
DOCUMENT NUMBER: 150:555189
TITLE: Renal dysfunction during and after high-dose methotrexate
AUTHOR(S): Green, Myke R.; Chamberlain, Marc C.
CORPORATE SOURCE: Department of Pharmacy, Intermountain Healthcare Corporation, Salt Lake City, UT, USA
SOURCE: Cancer Chemotherapy and Pharmacology (2009), 63(4), 599-604
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose: To evaluate renal dysfunction in adult patients encountered during and immediately after repeated administrations of high-dose methotrexate (HDMTX) for treatment of primary central nervous system lymphoma (PCNSL). Methods: In this single-center, retrospective, open label trial, 23 consecutive adult patients aged between 19 and 94 years diagnosed with PCNSL were given ≥4 consecutive cycles of HDMTX (8 gm/m2/dose) every 14 days as per institution protocol. Serum creatinine and serum methotrexate levels were measured at 24, 48 and 72 h after beginning of HDMTX infusion. Results: Forty-eight percent of all patients (30% of all HDMTX cycles) experienced a ≥200% increase in baseline creatinine during treatment. Nine percent of patients met requirements for administration of carboxypeptidase-G2 (glucarpidase) under compassionate use from National Cancer Institute. Thirty percent of patients at the conclusion of HDMTX therapy demonstrated a NCI Common Toxicity Criteria (CTC) grade 2 or higher increase in post-treatment serum creatinine compared to pre-treatment serum creatinine amongst whom ten patients (43%) had levels outside of the normal range. Conclusion: Renal dysfunction of CTC grade 2, 3 or 4 is common during treatment with HDMTX in the treatment of PCNSL, occurring in 40% of all cycles. Renal dysfunction persists at least 4 mo following the conclusion of therapy in nearly 30% of patients. Male patients age greater than 50 years are at greatest risk of renal dysfunction.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD

(5 CITINGS)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2008:1416057 HCAPLUS
DOCUMENT NUMBER: 150:506230
TITLE: Severe acute renal failure following high-dose methotrexate therapy in adults with haematological malignancies: a significant number result from unrecognized co-administration of several drugs
AUTHOR(S): de Miguel, Dunia; Garcia-Suarez, Julio; Martin, Yolanda; Gil-Fernandez, Juan Jose; Burgaleta, Carmen
CORPORATE SOURCE: Service of Haematology, Department of Medicine, Principe de Asturias University Hospital, University of Alcala, Alcala de Henares, Madrid, 28805, Spain
SOURCE: Nephrology, Dialysis, Transplantation (2008), 23(12), 3762-3766
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study aims to further define the incidence, predisposing factors and outcome of severe acute renal failure (ARF) occurring after high-dose methotrexate (HDMTX) therapy in adults with hematol. malignancies. Clin. data of all patients with hematol. malignancies treated with HDMTX between Jan. 2002 and July 2007 were retrospectively reviewed. A total of 158 courses of HDMTX (in 31 patients) were administered. During the study period, two cases (6.4%) of HDMTX-induced severe ARF occurred. Initially, the two patients showed markedly increased MTX concns. without apparent risk factors. However, when both cases were reviewed in retrospect, a potential drug interaction between HDMTX and either piperacillin-tazobactam (patient 1) or gemfibrozil (patient 2) were found.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2009:58653 HCAPLUS
DOCUMENT NUMBER: 150:555164
TITLE: Early recognition of renal toxicity of high-dose methotrexate therapy: A case report
AUTHOR(S): Nowicki, Theodore Scott; Bjornard, Kari; Kudlowitz, David; Sandoval, Claudio; Jayabose, Somasundaram
CORPORATE SOURCE: Division of Pediatric Hematology-Oncology, Department of Pediatrics, New York Medical College, Maria Fareri Children's Hospital, Valhalla, NY, USA
SOURCE: Journal of Pediatric Hematology/Oncology (2008), 30(12), 950-952
CODEN: JPHOFG; ISSN: 1077-4114
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A 10-yr-old boy with osteosarcoma and normal renal function manifested laboratory evidence of impending renal toxicity and extreme elevation of aspartate aminotrasferase and alanine aminotransferase within 2 h after the completion of a 4-h infusion of high-dose methotrexate (MTX) (12 g/m2), and went on to develop acute renal failure with life-threatening hyperkalemia 29 h later. Although his renal function recovered completely with high-dose leucovorin, hemodialysis, charcoal hemoperfusion, and carboxypeptidase G2, we present this case to emphasize that signs of renal toxicity may be present as early as 2 h after the completion of a 4-h MTX infusion, and to suggest that monitoring for MTX

toxicity should perhaps begin within a few hours after the completion of 4-h MTX infusion.
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2007:197850 HCAPLUS
DOCUMENT NUMBER: 146:267898
TITLE: Methods for construction of a library of optical antibody-based biosensors for use in diagnosis and therapy
INVENTOR(S): Wright, Michael John; Deonarain, Mahendra Persaud
PATENT ASSIGNEE(S): Imperial College Innovations Limited, UK
SOURCE: U.S. Pat. Appl. Publ., 39pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070042399	A1	20070222	US 2006-426265	20060623
PRIORITY APPLN. INFO.:			US 2005-693282P P	20050623

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The invention relates to methods for construction of a library of optical antibody-based biosensors for use in diagnosis and therapy. The library comprises a plurality of chelating ligand pairs, namely two antibodies or antibody fragments that bind specifically to distinct epitopes on the same target mol. wherein the two antibodies of each ligand pair are joined by a linker. The library comprises linkers of variable length and variable amino acid composition The method involves creating a library of linkers using PCR and cloning, followed by library selection using phage display. Two antibodies are linked with a library of linkers (randomized in length and sequence), including multiple pairs of ligands (multi-CRAb libraries). This approach circumvents the time-consuming and costly approach of determining 3D structures of each antigen-ligand complex, followed by mol. modeling to calculate the correct linker length, followed by mol. cloning.

L11 ANSWER 7 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2007:898578 HCAPLUS
DOCUMENT NUMBER: 148:69504
TITLE: Successful carboxypeptidase G2 rescue of a high-risk elderly Hodgkin lymphoma patient with methotrexate intoxication and renal failure
AUTHOR(S): Sieniawski, Michal; Rimpler, Matthaeus; Herrmann, Richard; Josting, Andreas
CORPORATE SOURCE: Department I of Internal Medicine, University of Cologne, Cologne, Germany
SOURCE: Leukemia & Lymphoma (2007), 48(8), 1641-1643
CODEN: LELYEA; ISSN: 1042-8194
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A case report of an elderly man who was successfully treated with CPDG2 after developing renal failure and MTX-associated toxicity refractory to leucovorin rescue. This case report confirms that CPDG2 is a highly effective treatment option for MTX intoxication can be safely used in high-risk elderly patients.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD

(1 CITINGS)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2008:28021 HCAPLUS
DOCUMENT NUMBER: 149:462215
TITLE: Glucarpidase (carboxypeptidase G2) intervention in adult and elderly cancer patients with renal dysfunction and delayed methotrexate elimination after high-dose methotrexate therapy
AUTHOR(S): Schwartz, Stefan; Borner, Klaus; Mueller, Krystina; Martus, Peter; Fischer, Lars; Korfel, Agnieszka; Auton, Timothy; Thiel, Eckhard
CORPORATE SOURCE: Medizinische Klinik III, Charite, Berlin, Germany
SOURCE: Oncologist (2007), 12(11), 1299-1308
CODEN: OCOLF6; ISSN: 1083-7159
PUBLISHER: AlphaMed Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: Leucovorin and extracorporeal removal of methotrexate (MTX) have limited efficacy in delayed MTX elimination after high-dose methotrexate (HD-MTX) therapy. Glucarpidase (carboxypeptidase G2) cleaves MTX into nontoxic metabolites, but experience with this enzyme is limited in adult patients. The authors evaluated the effects of glucarpidase intervention in adult and elderly patients with delayed MTX elimination. Patients and Methods: Forty-three patients (age, 18-78 years) with MTX serum concns. (sMTX) of 1-1187 μmol/l received glucarpidase, leucovorin rescue guided by MTX immunoassay, and standard supportive care. MTX and MTX metabolites were quantified in serum (24 patients) and urine (8 patients) by HPLC. Contributory risk factors, toxicities, and survival were recorded in all patients. Results: Glucarpidase was well tolerated and resulted in an immediate >97% reduction in sMTX, with a 0.2%-35% urinary recovery of the total MTX dose as inactive MTX metabolites. Forty (93%) of 43 patients had normalization (n = 25) or improvement (n = 15) of their serum creatinine. Frequent grade III-IV MTX toxicities were hematol. (60%) and mucositis (35%); only eight (19%) patients developed grade III-IV nephrotoxicity. Ten (23%) of 43 patients experienced fatal complications associated with HD-MTX therapy. Patients with three or more contributory risk factors for delayed MTX elimination had a significantly poorer survival than patients with fewer than three risk factors (hazard ratio, 3.64; confidence interval, 1.14-17.54). Conclusions: Glucarpidase is well tolerated and produces a rapid inactivation of substantial amts. of MTX. However, overall results are still unsatisfactory in adult and elderly patients, suggesting that earlier recognition of delayed MTX elimination and more rapid intervention are needed.
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2007:900372 HCAPLUS
DOCUMENT NUMBER: 147:335796
TITLE: Severe methotrexate toxicity precipitated by intravenous radiographic contrast
AUTHOR(S): Harned, Theresa M.; Mascarenhas, Leo
CORPORATE SOURCE: Division of Hematology/Oncology, Childrens Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
SOURCE: Journal of Pediatric Hematology/Oncology (2007),

29(7), 496-499
CODEN: JPHOFG; ISSN: 1077-4114
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Methotrexate (MTX), a widely used anticancer agent, and i.v. iodinated contrast used for radiog. studies can both cause acute renal failure. Their combined exposure may place patients at higher risk for renal failure. This report describes 2 pediatric patients with MTX toxicity precipitated by the use of i.v. radiog. contrast. One patient recovered with leucovorin rescue therapy, whereas the second patient responded to carboxypeptidase-G2. Both patients suffered MTX-related toxicities including myelosuppression and mucositis, but recovered full renal function and tolerated further high-dose MTX therapy. These cases suggest that i.v. iodinated contrast should be avoided in patients receiving high-dose MTX.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2008:329710 HCAPLUS
DOCUMENT NUMBER: 149:298463
TITLE: Optimal management of acute methotrexate intoxication
AUTHOR(S): Balloy, T.; Desroches, M.-C.; Moussay, C.; Merkadal, C.; Fernandez, C.; Farinotti, R.
CORPORATE SOURCE: Service de Pharmacie, Hopital La Pitie-Salpetriere, Assistance Publique-Hopitaux de Paris, Paris, 75651, Fr.
SOURCE: Journal de Pharmacie Clinique (2007), 26(4), 253-260
CODEN: JPCLDE; ISSN: 0291-1981
PUBLISHER: John Libbey Eurotext
DOCUMENT TYPE: Journal; General Review
LANGUAGE: French
AB A review. Methotrexate is a folate analog that inhibits the enzyme dihydrofolate reductase. At high doses it is an important component of treatment for malignancies. At lower doses, methotrexate is a widely used disease-modifying anti-rheumatic drug. In both cases, methotrexate can lead to nephrotoxicity and delayed elimination with development of life-threatening toxicity. Hence, high-dose methotrexate treatments require previous intensive hyperhydratation and urine alkalinization. Therapeutic drug monitoring is also recommended to follow methotrexate elimination and leucovorin rescue. Life-threatening toxicity requires effective methotrexate clearance via high-flux hemodialysis or hemofiltration. Efficiency of these techniques is dependent upon methotrexate blood levels and, therefore, subject to high intra-individual variability. Moreover, post-dialysis "rebound" of the serum methotrexate concns. were reported. More recently, the use of carboxypeptidase G2 was reported in methotrexate toxicity management. Carboxypeptidase G2 enzymically degrades methotrexate and rapidly reduces high serum concns. of methotrexate in a 97 to 98.7% rate within one hour following administration, according to different authors. Differences between methods and outcomes of literature reports make comparisons difficult. To date, no trial has compared dialysis vs. carboxypeptidase G2 efficiency. This paper addresses methotrexate toxicity management, comparing efficiency and applications of dialysis and carboxypeptidase G2 administration.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2006:1063109 HCAPLUS
DOCUMENT NUMBER: 145:413661
TITLE: Stably tethered structures of defined composition with multiple functions or binding specificities for disease diagnosis and treatment
INVENTOR(S): Chang, Chien Hsing; Goldenberg, David M.; McBride, William J.; Rossi, Edmund A.
PATENT ASSIGNEE(S): IBC Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 166 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 25
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006107786	A2	20061012	WO 2006-US12084	20060329
WO 2006107786	A3	20080807		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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US 7521056	B2	20090421	US 2006-391584	20060328
US 20060228300	A1	20061012		
AU 2006232310	A1	20061012	AU 2006-232310	20060329
CA 2604034	A1	20061012	CA 2006-2604034	20060329
EP 1874358	A2	20080109	EP 2006-758249	20060329
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JP 2008542194	T	20081127	JP 2008-505395	20060329
US 20070086942	A1	20070419	US 2006-478021	20060629
US 7534866	B2	20090519		
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CA 2607056	A1	20070426	CA 2006-2607056	20060629
WO 2007046893	A2	20070426	WO 2006-US25499	20060629
WO 2007046893	A3	20090423		
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EP 1937851	A2	20080702	EP 2006-785922	20060629
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JP 2009517337 T 20090430 JP 2008-536564 20060629
US 20070087001 A1 20070419 US 2006-581287 20061016
US 7642239 B2 20100105
AU 2006304418 A1 20070426 AU 2006-304418 20061016
CA 2625992 A1 20070426 CA 2006-2625992 20061016
WO 2007047609 A2 20070426 WO 2006-US40431 20061016
WO 2007047609 A3 20090319
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EP 1937724 A2 20080702 EP 2006-826058 20061016
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JP 2009514813 T 20090409 JP 2008-536725 20061016
US 20070140966 A1 20070621 US 2006-633729 20061205
US 7527787 B2 20090505
AU 2006330051 A1 20070705 AU 2006-330051 20061205
CA 2633486 A1 20070705 CA 2006-2633486 20061205
WO 2007075270 A2 20070705 WO 2006-US46367 20061205
WO 2007075270 A3 20080306
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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
EP 1959993 A2 20080827 EP 2006-848816 20061205
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS

JP 2009519931 T 20090521 JP 2008-545643 20061205
SG 153825 A1 20090729 SG 2009-4095 20061205
IN 2007DN07640 A 20071109 IN 2007-DN7640 20071004
US 20090060862 A1 20090305 US 2007-925408 20071026
US 7666400 B2 20100223
CN 101534865 A 20090916 CN 2006-80019869 20071204
CN 101583376 A 20091118 CN 2006-80019839 20071204
KR 2008055932 A 20080619 KR 2008-709357 20080418
CN 101534849 A 20090916 CN 2006-80039268 20080421
IN 2008DN03448 A 20080725 IN 2008-DN3448 20080425
IN 2008DN04630 A 20080815 IN 2008-DN4630 20080529
KR 2008097995 A 20081106 KR 2008-717349 20080716
CN 101374546 A 20090225 CN 2006-80052809 20080814
US 20090269277 A1 20091029 US 2009-396605 20090303

US 20090202433	A1	20090813	US 2009-417917		20090403
PRIORITY APPLN. INFO.:			US 2005-668603P	P	20050406
			US 2005-728292P	P	20051019
			US 2005-751196P	P	20051216
			US 2006-782332P	P	20060314
			US 2006-391584	A	20060328
			US 2005-389358	A2	20060324
			US 2006-389358	A2	20060324
			WO 2006-US10762	A	20060324
			WO 2006-US12084	W	20060329
			US 2005-478021	A2	20060629
			US 2006-478021	A2	20060629
			WO 2006-US25499	W	20060629
			WO 2006-US40431	W	20061016
			US 2006-864530P	P	20061106
			US 2006-633729	A2	20061205
			WO 2006-US46367	W	20061205

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention concerns methods and compns. for stably tethered structures of defined compns. with multiple functionalities and/or binding specificities. Particular embodiments concern stably tethered structures comprising a homodimer of a first monomer, comprising a dimerization and docking domain (DDD) attached to a first precursor, and a second monomer comprising an anchoring domain (AD) attached to a second precursor. The first and second precursors may be virtually any mol. or structure, such as antibodies, antibody fragments, antibody analogs or mimetics, aptamers, binding peptides, fragments of binding proteins, known ligands for proteins or other mols., enzymes, detectable labels or tags, therapeutic agents, toxins, pharmaceuticals, cytokines, interleukins, interferons, radioisotopes, proteins, peptides, peptide mimetics, polynucleotides, RNAi, oligosaccharides, natural or synthetic polymeric substances, nanoparticles, quantum dots, organic or inorg. compds., etc. The disclosed methods and compns. provide a simple, easy to purify way to obtain any binary compound attached to any monomeric compound, or any trinary compound Thus, an anti-CEA Fab fused to a DDD sequence from the regulatory subunit of cAMP-dependent protein kinase was prepared with transgenic cells and shown to form dimers. The stability of these dimers can be increased by, for example, incorporating cysteine residues into the DDD peptide such that, when the dimer is formed, the cysteine residues are brought into proximity and can thereby form disulfide bonds. To demonstrate that these Fab dimers may be used to "pretarget" tumor cells, the dimers were injected into tumor-bearing mice and were shown to concentrate at the site of the tumor. Injection of a peptide containing an A kinase anchoring protein peptide (AD) which is fused to an imaging agent or therapeutic agent is expected to lead to localization of this conjugate at the tumor due to interaction of the AD and DDD domains.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L11 ANSWER 12 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER:	2006:1152964 HCAPLUS
DOCUMENT NUMBER:	146:113879
TITLE:	Understanding and managing methotrexate nephrotoxicity
AUTHOR(S):	Widemann, Brigitte C.; Adamson, Peter C.
CORPORATE SOURCE:	Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD, USA
SOURCE:	Oncologist (2006), 11(6), 694-703 CODEN: OCOLF6; ISSN: 1083-7159
PUBLISHER:	AlphaMed Press
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

AB A review. Methotrexate (MTX) is one of the most widely used anticancer

agents, and administration of high-dose methotrexate (HDMTX) followed by leucovorin (LV) rescue is an important component in the treatment of a variety of childhood and adult cancers. HDMTX can be safely administered to patients with normal renal function by the use of alkalinization, hydration, and pharmacokinetically guided LV rescue. Despite these measures, HDMTX-induced renal dysfunction continues to occur in approx. 1.8% of patients with osteosarcoma treated on clin. trials. Prompt recognition and treatment of MTX-induced renal dysfunction are essential to prevent potentially life-threatening MTX-associated toxicities, especially myelosuppression, mucositis, and dermatitis. In addition to conventional treatment approaches, dialysis-based methods have been used to remove MTX with limited effectiveness. More recently carboxypeptidase-G2 (CPDG2), a recombinant bacterial enzyme that rapidly hydrolyzes MTX to inactive metabolites, has become available for the treatment of HDMTX-induced renal dysfunction. CPDG2 administration has been well tolerated and resulted in consistent and rapid redns. in plasma MTX concns. by a median of 98.7% (range, 84%-99.5%). The early administration of CPDG2 in addition to LV may be beneficial for patients with MTX-induced renal dysfunction and significantly elevated plasma MTX concns.

OS.CITING REF COUNT: 29 THERE ARE 29 CAPLUS RECORDS THAT CITE THIS RECORD (29 CITINGS)

REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:330956 HCAPLUS

DOCUMENT NUMBER: 142:475555

TITLE: Intrathecal methotrexate neurotoxicity: clinical correlates and antidotal treatment

AUTHOR(S): Finkelstein, Yoram; Zevin, Shoshana; Raikhlin-Eisenkraft, Bianca; Bentur, Yedidia

CORPORATE SOURCE: Department of Neurology, Shaare Zedek Medical Center and Faculty of Health Sciences, Ben-Gurion University, Jerusalem, 91031, Israel

SOURCE: Environmental Toxicology and Pharmacology (2005), 19(3), 721-725
CODEN: ETOPFR; ISSN: 1382-6689

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The neurotoxicity of methotrexate (MTX) is more severe when administered intrathecally (IT) than by the oral and i.v. routes, and was reported even with a single administration of therapeutic doses of 12 or 15 mg. Prompt recognition and treatment are essential to improve the outcome after massive IT-MTX overdose. Treatment options include CSF drainage or CSF exchange, ventriculolumbar perfusion, IT corticosteroids to reduce CSF inflammation and i.v. leucovorin to reduce systemic toxicity. Toxicity resulting from IT injection of leucovorin is controversial. CSF drainage and exchange are particularly effective if performed soon after the overdose. In this paper the authors describe a protocol of treatment for severe cases of IT-MTX overdose in excess of 100 mg. The mainstay of treatment is dilution and removal from CSF of excessive methotrexate alongside with specific antidotal therapy.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 14 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:111436 HCAPLUS

DOCUMENT NUMBER: 142:423408

TITLE: Carboxypeptidase G2 rescue in patients with methotrexate intoxication and renal failure

AUTHOR(S): Buchen, S.; Ngampolo, D.; Melton, R. G.; Hasan, C.; Zoubek, A.; Henze, G.; Bode, U.; Fleischhack, G.
CORPORATE SOURCE: Department of Paediatric Haematology/Oncology, Children's Medical Hospital, University of Bonn, Bonn, Germany
SOURCE: British Journal of Cancer (2005), 92(3), 480-487 CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The methotrexate (MTX) rescue agent carboxypeptidase G2 (CPDG2) rapidly hydrolyzes MTX to the inactive metabolite DAMPA (4-[[2,4-diamino-6-(pteridinyl)methyl]-methylamino]-benzoic acid) and glutamate in patients with MTX-induced renal failure and delayed MTX excretion. DAMPA is thought to be an inactive metabolite of MTX because it is not an effective inhibitor of the MTX target enzyme dihydrofolate reductase. DAMPA is eliminated more rapidly than MTX in these patients, which suggests a nonrenal route of elimination. In a phase II study (May 1997-Mar. 2002), CPDG2 was administered i.v. to 82 patients at a median dose of 50 U kg-1 (range 33-60 U kg-1). Eligible patients for this study had serum MTX concns. of >10 μM at 36 h or >5 μM at 42 h after start of MTX infusion and documented renal failure (serum creatinine ≥1.5 times the upper limit of normal). Immediately before CPDG2 administration, a median MTX serum level of 11.93 μM (range 0.52-901 μM) was documented. Carboxypeptidase G2 was given at a median of 52 h (range 25-178 h) following the start of an MTX infusion of 1-12 g m-2 4-36 h-1 and resulted in a rapid 97% (range 73-99%) reduction of the MTX serum level. Toxicity related to CPDG2 was not observed Toxicity related to MTX was documented in about half the patients; four patients died despite CPDG2 administration due to severe myelosuppression and septic complications. In conclusion, administration of CPDG2 is a well-tolerated, safe and a very effective way of MTX elimination in delayed excretion due to renal failure.
OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 15 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2005:149163 HCAPLUS
DOCUMENT NUMBER: 143:722
TITLE: Interactions of carboxypeptidase G2 with 6S-leucovorin and 6R-leucovorin in vitro: implications for the application in case of methotrexate intoxications
AUTHOR(S): Hempel, Georg; Lingg, Rainer; Boos, Joachim
CORPORATE SOURCE: Paediatrische Haematologie und Onkologie, Klinik und Poliklinik fuer Kinder- und Jugendmedizin, Munster, 58-62,48149, Germany
SOURCE: Cancer Chemotherapy and Pharmacology (2005), 55(4), 347-353 CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Carboxypeptidase G2 (CPG2) is used when unexpected toxicity or renal failure occurs during high-dose methotrexate therapy. Leucovorin is also administered to antagonize the effects of methotrexate on purine anabolism. To investigate the effects of CPG2 on leucovorin rescue, we incubated the enzyme with both stereoisomers and analyzed the degradation A method for separating the stereoisomers of leucovorin, the internal

standard aminopterin and the degradation products by capillary electrophoresis with 2.6-dimethyl-β-cyclodextrin as a chiral selector has been developed. The active 6S-leucovorin is degraded much faster than the inactive 6R-isomer. The maximum observed degradation velocity was 31 μM/min for 6S-leucovorin and 20 μM/min for 6R-leucovorin, resp., with an initial concentration of each stereoisomer of 250 μM. Similar results were obtained at lower concns. of leucovorin isomers. Thus, the selectivity of CPG2 for methotrexate in comparison to leucovorin is not as high as anticipated in the literature as only the active 6S-leucovorin and not the mixture of the diastereomers should be taken into account. We conclude that the protective effects of leucovorin are antagonized by CPG2. Therefore, CPG2 should be administered to patients with caution.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 16 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2004:493868 HCAPLUS

DOCUMENT NUMBER: 141:52866

TITLE: A variant of a single-chain antibody to p97 melanotransferrin with increased stability for use in diagnosis and therapy of melanoma

INVENTOR(S): McDonagh, Charlotte F.; Francisco, Joseph A.

PATENT ASSIGNEE(S): Seattle Genetics, Inc., USA

SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004050867	A1	20040617	WO 2002-US38414	20021202
W: CA, US				
US 20060160174	A1	20060720	US 2005-537143	20051024

PRIORITY APPLN. INFO.: WO 2002-US38414 W 20021202

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A variant of the L49 single chain antibody (L49-sFv) to p97 melanotransferrin that shows increased refolding efficiency and greater stability in mouse serum, and substantially maintaining binding affinity for p97 melanotransferrin is described. P97 melanotransferrin is expressed on the surface of a number of types of cancer (carcinoma) cells, e.g., melanoma cells, lung cancer cells, renal cancer cells, colon cancer cells, and so may be useful in diagnosis and therapy. The present invention also relates to a modified L49-sFv fused or conjugated to a therapeutic agent, such as a cytotoxic mol. or a pro-drug converting enzyme. The present invention also relates to methods of using the modified L49-sFv mols. fused or conjugated to a therapeutic agent for treatment and/or prophylaxis of cancer, which cancer cells express p97 melanotransferrin. Unusual amino acids predicted to affect stability of the antibody were identified by sequence alignment. These amino acids were substituted with the most common amino acids at these sites and the ability of the substitution variant to bind the antigen was tested. Substitution of three amino acids in the VH region led to the most complete refolding of the antibody. The substitution variants showed binding affinities for melanotransferrin comparable to those of the original single-chain antibody.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 17 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2004:459829 HCAPLUS
DOCUMENT NUMBER: 141:81926
TITLE: High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma: incidence, treatment, and outcome
AUTHOR(S): Widemann, Brigitte C.; Balis, Frank M.; Kempf-Bielack, Beate; Bielack, Stefan; Pratt, Charles B.; Ferrari, Stefano; Bacci, Gaetano; Craft, Alan W.; Adamson, Peter C.
CORPORATE SOURCE: Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD, USA
SOURCE: Cancer (New York, NY, United States) (2004), 100(10), 2222-2232
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB High-dose methotrexate (HDMTX)-induced renal dysfunction can be life threatening, because it delays methotrexate (MTX) excretion, thereby exacerbating the other toxicities of MTX. HDMTX-induced nephrotoxicity has been managed with high-dose leucovorin, dialysis-based methods of MTX removal, thymidine, and with the recombinant enzyme, carboxypeptidase-G2 (CPDG2), which cleaves MTX to inactive metabolites. The objectives of the current study were to estimate the current incidence of HDMTX-induced renal dysfunction in patients with osteosarcoma and to compare the efficacy and recovery of renal function for dialysis-based methods of MTX removal with treatment using CPDG2. The literature was reviewed for osteosarcoma trials, use of dialysis-based methods for MTX removal, and reports of MTX-induced nephrotoxicity, including information regarding recovery of renal function. Clin. trial databases of select osteosarcoma studies were reviewed. The efficacy of CPDG2 and renal recovery after CPDG2 rescue was obtained from the database of a compassionate-release trial. Approx. 1.8% of patients with osteosarcoma (68 of 3887 patients) who received HDMTX developed nephrotoxicity Grade ≥ 2. The mortality rate among those patients was 4.4% (3 of 68 patients). Dialysis-based methods of MTX removal were used frequently but had limited effectiveness in removing MTX compared with the rapid redns. > 98% in plasma MTX concns. achieved with CPDG2. CPDG2 did not appear to increase the time to recovery of renal function compared with supportive treatment that included dialysis-based methods. HDMTX-induced renal dysfunction continues to occur in approx. 1.8% of patients with osteosarcoma who are treated on clin. protocols with optimal supportive care. For patients with delayed MTX excretion and high plasma MTX concns., CPDG2 should be considered over hemodialysis to lower plasma MTX concns. rapidly and efficiently.
OS.CITING REF COUNT: 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)
REFERENCE COUNT: 103 THERE ARE 103 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 18 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2004:887160 HCAPLUS
DOCUMENT NUMBER: 142:191108
TITLE: Treatment of accidental intrathecal methotrexate overdose With intrathecal carboxypeptidase G2
AUTHOR(S): Widemann, Brigitte C.; Balis, Frank M.; Shalabi, Aiman; Boron, Matthew; O'Brien, Michelle; Cole, Diane E.; Jayaprakash, Nalini; Ivy, Percy; Castle, Valerie;

Muraszko, Karin; Moertel, Christopher L.; Trueworthy, Robert; Hermann, Robert C.; Moussa, Ali; Hinton, Stuart; Reaman, Gregory; Poplack, David; Adamson, Peter C.

CORPORATE SOURCE: Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD, USA

SOURCE: Journal of the National Cancer Institute (2004), 96(20), 1557-1559
CODEN: JNCIEQ; ISSN: 0027-8874

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The bacterial enzyme carboxypeptidase G2 (CPDG2) rapidly hydrolyzes methotrexate to inactive metabolites. We administered recombinant CPDG2 (2000 U) intrathecally to seven cancer patients 3 to 9 h after they had received an accidental overdose of intrathecal methotrexate (median dose = 364 mg; range = 155-600 mg). Four of the seven patients had cerebrospinal fluid (CSF) exchange to remove methotrexate before CPDG2 administration. Immediate symptoms of the methotrexate overdoses included seizures (n = 5), coma (n = 2), and cardiopulmonary compromise (n = 2). Before CPDG2 administration, the median concns. of methotrexate in CSF were 264 μM (range = 97-510 μM) among patients who had CSF exchange and 8050 μM (range = 2439-16 500 μM) among patients who did not. After intrathecal CPDG2 administration, methotrexate concns. in CSF declined by more than 98%. All patients recovered completely from the intrathecal methotrexate overdose except for two patients who had memory impairments. Antibodies to CPDG2 were not detected in plasma after treatment with intrathecal CPDG2. Intrathecal CPDG2 is well tolerated, rapidly decreases CSF methotrexate concns., and appears to be efficacious for treating accidental intrathecal methotrexate overdoses.

OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 19 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:874544 HCAPLUS

DOCUMENT NUMBER: 137:362990

TITLE: Carboxypeptidase-G2 rescue in cancer patients with delayed methotrexate elimination after high-dose methotrexate therapy

AUTHOR(S): Krause, Anke S.; Weihrauch, Martin R.; Bode, Udo; Fleischhack, Gudrun; Elter, Thomas; Heuer, Theodor; Engert, Andreas; Diehl, Volker; Josting, Andreas

CORPORATE SOURCE: Department of Internal Medicine I, University of Cologne, Cologne, Germany

SOURCE: Leukemia & Lymphoma (2002), 43(11), 2139-2143
CODEN: LELYEA; ISSN: 1042-8194

PUBLISHER: Taylor & Francis Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB High-dose methotrexate (HDMTX) is a component of many cancer treatment regimens. Despite careful management, delayed renal clearance, followed by extremely high serum levels with potentially life-threatening toxicity can occur. In the present study, we report our results of carboxypeptidase-G2 (CPDG2) rescue in 8 patients with delayed methotrexate elimination and renal impairment after HDMTX therapy for lymphoma or osteosarcoma. A dose of 50 U/kg CPDG2 was administered. MTX plasma levels decreased rapidly and recovery of renal function was observed in all patients. No patient developed severe WHO grade 4 MTX toxicity. CPDG2 provides an alternative route of MTX elimination by converting it to inactive and non-toxic metabolites. CPDG2 rescue was

well tolerated, safe and very effective in preventing severe or life-threatening MTX toxicity.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 20 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1997:461628 HCAPLUS

DOCUMENT NUMBER: 127:104332

ORIGINAL REFERENCE NO.: 127:19946h,19947a

TITLE: Cell-targeted cytotoxic drug therapy system, and preparation of associated compounds

INVENTOR(S): Khan, Tariq

PATENT ASSIGNEE(S): Aepact Limited, UK; Khan, Tariq

SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9720580	A1	19970612	WO 1996-GB3000	19961206
W: CA, GB, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2239203	A1	19970612	CA 1996-2239203	19961206
EP 865298	A1	19980923	EP 1996-940685	19961206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000502071	T	20000222	JP 1997-521082	19961206
PRIORITY APPLN. INFO.:			GB 1995-24942 A	19951206
			WO 1996-GB3000 W	19961206

OTHER SOURCE(S): MARPAT 127:104332

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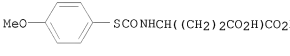


I

AB A therapeutic system is disclosed which comprises (a) a compound comprising a target cell-specific portion (e.g. an antibody) and a portion capable of converting a substance into another substance (e.g. an enzyme); and (b) a mol. capable of substantially inhibiting the conversion of the substance, or a precursor of the mol. In one particularly preferred embodiment, the other substance is cytotoxic and the substance is substantially noncytotoxic, the system further comprising the substance. In a second particularly preferred embodiment, the substance, in its native state, is able to inhibit the effect of a cytotoxic agent and the other substance has less effect against said cytotoxic agent, the system further comprising (a) a cytotoxic agent and (b) the substance. Preparation of carboxypeptidase G2 inhibitors, e.g. In-1 (I), is described, as is e.g. the effect of I on the enzyme activity of carboxypeptidase G2 conjugated to the F(ab)2 fragment of anti-carcinoembryonic antigen monoclonal antibody A5B7. The drug therapy system of the invention is useful for treatment of tumors.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 21 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1997:344878 HCAPLUS
DOCUMENT NUMBER: 127:13129
ORIGINAL REFERENCE NO.: 127:2535a,2538a
TITLE: Carboxypeptidase-G2, thymidine, and leucovorin rescue in cancer patients with methotrexate-induced renal dysfunction
AUTHOR(S): Widemann, Brigitte C.; Balis, Frank M.; Murphy, Robert F.; Sorensen, J. Mel; Montello, Michael J.; O'Brien, Michelle; Adamson, Peter C.
CORPORATE SOURCE: Pediatric Branch Cancer Therapy Evaluation Program, Natl. Cancer Inst., Natl. Inst. Health, Bethesda, MD, USA
SOURCE: Journal of Clinical Oncology (1997), 15(5), 2125-2134 CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Methotrexate nephrotoxicity can lead to delayed methotrexate elimination and the development of life-threatening toxicity, which may not be preventable with the standard rescue agent leucovorin. In preclin. studies, we previously demonstrated that carboxypeptidase-G2 (CPDG2) rapidly hydrolyzes methotrexate to nontoxic metabolites. A protocol for the compassionate use of CPDG2 in patients who develop nephrotoxicity while receiving high-dose methotrexate was therefore developed. The pharmacol. and clin. outcome of CPDG2 rescue administered with thymidine and leucovorin in 20 patients is presented here. Patients with high-dose methotrexate-induced renal dysfunction received one to three doses of CPDG2, 50 U/kg body weight i.v. (IV), thymidine 8 g/m2 by continuous IV infusion, and standard pharmacokinetically guided leucovorin rescue. Plasma concns. of methotrexate and its inactive metabolite 4-deoxy-4-amino-N10-methylpteroic acid (DAMPA) were measured before and after CPDG2 using high-pressure liquid chromatog. (HPLC). Tolerance of CPDG2 and thymidine, development of methotrexate toxicities, and recovery of renal function were monitored. Twenty patients who received high-dose methotrexate for osteosarcoma (n = 11), lymphoid cancers (n = 8),and gastric cancer (n = 1) developed nephrotoxicity (median serum creatinine, 3.2 mg/dL) and elevated plasma methotrexate concns. (median, 201 μmol/L at hour 46). CPDG2 and thymidine rescue was well tolerated and resulted in a rapid 95.6% to 99.6% reduction in the plasma methotrexate concentration Methotrexate-related toxicity was mild to moderate. Serum creatinine returned to normal values at a median of 22 days. CPDG2, thymidine, and leucovorin rescue was highly effective in 20 patients at high risk for developing life-threatening methotrexate toxicity after the onset of methotrexate-induced nephrotoxicity and delayed methotrexate excretion.
OS.CITING REF COUNT: 30 THERE ARE 30 CAPLUS RECORDS THAT CITE THIS RECORD (30 CITINGS)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 22 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1996:551361 HCAPLUS
DOCUMENT NUMBER: 125:204498
ORIGINAL REFERENCE NO.: 125:38101a,38104a
TITLE: Methods and compositions for gene therapy of solid tumors in vivo
INVENTOR(S): Burrows, Francis J.; Fong, Timothy C.; Polo, John M.;

Dubensky, Thomas W., Jr.; Jolly, Douglas J.
PATENT ASSIGNEE(S): Chiron Viagene, Inc., USA
SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9621416	A2	19960718	WO 1995-US16855	19951222
WO 9621416	A3	19961010		

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

AU 9646082	A	19960731	AU 1996-46082	19951222
EP 802801	A2	19971029	EP 1995-944229	19951222

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE

JP 2001520503	T	20011030	JP 1996-521685	19951222
PRIORITY APPLN. INFO.:			US 1994-368574 A	19941230
			WO 1995-US16855 W	19951222

AB The present invention provides compns. and methods for treatment of solid tumors with gene therapy utilizing recombinant viral vectors that express polypeptides which (1) selectively initiate irreversible coagulation of blood in the tumor vasculature, (2) inhibit tumor neovascularization, (3) are capable of activating a non-toxic agent into a toxic agent within the tumor vascular wall causing destruction of the vascular bed, and (4) absorb or metabolize nutrients in the blood being supplied to the tumor. The production of these polypeptides by transduced cells in or adjacent to the blood vessels of the tumor result in the death of tumor cells.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 23 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1996:453058 HCAPLUS
DOCUMENT NUMBER: 125:131932
ORIGINAL REFERENCE NO.: 125:24401a,24404a
TITLE: Carboxypeptidase G2 rescue after high-dose methotrexate
AUTHOR(S): DeAngelis, Lisa M.; Tong, William P.; Lin, Silan; Fleisher, Martin; Bertino, Joseph R.
CORPORATE SOURCE: Departments Neurology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SOURCE: Journal of Clinical Oncology (1996), 14(7), 2145-2149
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study was a pilot project to assess the safety and efficacy of carboxypeptidase G2 (CPG2) rescue from high-dose (HD) methotrexate (MTX) in patients with recurrent cerebral lymphoma. Patients and Methods: Four patients with recurrent primary CNS lymphoma (PCNSL) were studied. Patients received 3.0 g/m2 MTX infused over 2 h. Twelve hours after the start of MTX, 50 U/kg CPG2 was infused; a second dose of CPG2 was given 6 h after the first. Blood and CSF were collected and assayed for levels of MTX, CPG2, and 2,4-diamino-N10-methylpteroic acid (DAMPA), a cleavage product of MTX after CPG2. Serum was collected for at

least 2 wk after administration of MTX-CPG2 to assess anti-CPG2 activity antibodies. Results: All patients had at least a 2-log decline in plasma MTX levels to the subtherapeutic range within 5 min of CPG2 administration. The second dose of CPG2 did not further diminish the already low plasma MTX level. DAMPA appeared and was detected as the plasma MTX concentration decreased. CSF MTX concentration remained elevated for 4 h after CPG2, and its decline followed first-order kinetics. Anti-CPG2 activity antibodies were not detected in any patient. No MTX or CPG2 toxicity was observed Conclusion: CPG2 rescue is a safe, effective alternative to leucovorin rescue after HD MTX and may prove particularly useful for the treatment of MTX-sensitive CNS tumors, as it does not affect CSF MTX levels.

OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)

L11 ANSWER 24 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1996:160401 HCAPLUS
DOCUMENT NUMBER: 124:250063
ORIGINAL REFERENCE NO.: 124:46009a,46012a
TITLE: Successful treatment of intrathecal methotrexate overdose by using ventriculolumbar perfusion and intrathecal instillation of carboxypeptidase G2
AUTHOR(S): O'Marcaigh, Aengus S.; Johnson, Christopher M.; Smithson, William A.; Patterson, Marc C.; Widemann, Brigitte C.; Adamson, Peter C.; McManus, Michael J.
CORPORATE SOURCE: Section Pediatric Hematology/Oncology, Mayo Clinic Rochester, Rochester, MN, 55905, USA
SOURCE: Mayo Clinic Proceedings (1996), 71(2), 161-5
CODEN: MACPAJ; ISSN: 0025-6196
PUBLISHER: Mayo Clinic Proceedings
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prompt and appropriate management measures are critical in order to achieve a favorable outcome after a major overdose of intrathecally (IT) administered methotrexate (MTX). Published information available to guide clinicians in the immediate management of this medical emergency is scant. Herein we describe a 6-yr-old boy with acute lymphoblastic leukemia who received an inadvertent overdose of 600 mg of IT administered MTX instead of the intended dose of 12 mg. Severe acute neurotoxicity developed rapidly. Lumbar puncture and drainage of 15 mL of cerebrospinal fluid 2 h after administration resulted in removal of 32% of the administered drug. Ventriculolumbar perfusion with 240 mL of warmed isotonic saline through ventricular and lumbar catheters for 3 h resulted in removal of a total of 90% of the drug within 81/2 h after administration. IT administration of 2,000 U of carboxypeptidase G2 (CPDG2), an enzyme that inactivates MTX, resulted in a further 150-fold reduction in cerebrospinal fluid MTX concentration The patient experienced complete recovery. To our knowledge, this is the first reported case of the use of IT instillation of CPDG2 for the treatment of an overdose of IT administered MTX in a human, and it is only the second reported favorable outcome after an IT overdose of more than 500 mg of MTX. Minor IT overdoses of MTX can be managed by immediate lumbar drainage alone. Major overdoses may also necessitate prompt ventriculolumbar perfusion, IT instillation of CPDG2, and further supportive measures for a successful outcome after this infrequent but potentially catastrophic event.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L11 ANSWER 25 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1996:23677 HCAPLUS

DOCUMENT NUMBER: 124:134480
ORIGINAL REFERENCE NO.: 124:24679a,24682a
TITLE: Successful carboxypeptidase G2 rescue in delayed MTX-elimination due to renal failure
AUTHOR(S): Hum, Martina; Kamen, Barton A.
CORPORATE SOURCE: Southwestern Medical Center, University Texas, Dallas, TX, 75235-9063, USA
SOURCE: Pediatric Hematology and Oncology (1995), 12(6), 521-4
CODEN: PHONEN; ISSN: 0888-0018
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 12 refs. on the use of leucovorin to abrogate methotrexate cytotoxicity, ELISA and overestimations of methotrexate,and alternatives to high-dose methotrexate.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L11 ANSWER 26 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1995:917172 HCAPLUS
DOCUMENT NUMBER: 124:21380
ORIGINAL REFERENCE NO.: 124:3895a,3898a
TITLE: Successful carboxypeptidase G2 rescue in delayed methotrexate elimination due to renal failure
AUTHOR(S): Zoubek, Andreas; Zaunschirm, Harald A.; Lion, Thomas; Fischmeister, Gustav; Vollnhofer, Georg; Gadner, Helmut; Pillwein, Konrad; Schalhorn, Andreas; Bode, Udo
CORPORATE SOURCE: St. Anna Children's Hospital, Vienna, A 1090, Austria
SOURCE: Pediatric Hematology and Oncology (1995), 12(5), 471-7
CODEN: PHONEN; ISSN: 0888-0018
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We report on an 18.5-yr-old woman with osteosarcoma and delayed methotrexate (MTX) elimination due to renal failure after high-dose MTX, in whom rescue with high doses of folinic acid caused intolerable side effects. In this life-threatening clin. situation, the patient was rescued by the administration of recombinant carboxypeptidase G2, a bacterial enzyme that rapidly hydrolyzes MTX into inactive metabolites. This is the first report on the successful clin. use of this alternative catabolic route for the elimination of MTX.
OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

L11 ANSWER 27 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1993:595659 HCAPLUS
DOCUMENT NUMBER: 119:195659
ORIGINAL REFERENCE NO.: 119:34661a,34664a
TITLE: Inactivation of cytotoxic drugs in cytotoxic drug therapy, and prodrug therapy kit
INVENTOR(S): Bagshawe, Kenneth Dawson
PATENT ASSIGNEE(S): UK
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9313806	A1	19930722	WO 1993-GB40	19930111
W: CA, GB, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 620742	A1	19941026	EP 1993-901821	19930111
R: DE, ES, FR, GB, IT, NL, SE				
JP 07506339	T	19950713	JP 1993-512252	19930111
GB 2276624	B	19941005	GB 1994-10237	19940523
GB 2276624	A	19941005		

PRIORITY APPLN. INFO.: GB 1992-415 A 19920109
GB 1992-4104 A 19920226
WO 1993-GB40 W 19930111

AB The invention relates to inactivation of cytotoxic drugs to limit their undesirable side effects in cytotoxic drug therapy. The title cytotoxic prodrug kit comprises three components: a 1st component containing a target cell-specific portion and an enzymically active portion; a 2nd component containing a cytotoxic prodrug portion convertible by the enzymically active portion to a cytotoxic drug; and a 3rd component containing a portion capable of at least partly restraining the component from leaving the vascular compartment of a host when the compound is administered to the vascular compartment, and an inactivating portion capable of converting the cytotoxic drug to a less toxic substance. Thus, a prodrug kit was prepared which comprises a 1st component containing antibody to carcinoembryonic antigen conjugated to carboxypeptidase A (CPA), a 2nd component containing Ala-methotrexate as prodrug, and a 3rd component containing carboxypeptidase G2 (CPG2) conjugated to dextran for confining CPG2 activity to the vascular compartment. To reduce enzyme activity at nontumor sites, a galactosylated anti-CPA monoclonal antibody (MAb) is given to eliminate enzyme activity in plasma, and then the nongalactosylated anti-CPA MAb is given to inactivate residual enzyme activity in other nontumor tissues.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 28 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1992:542841 HCAPLUS
DOCUMENT NUMBER: 117:142841
ORIGINAL REFERENCE NO.: 117:24537a,24540a
TITLE: Methotrexate pharmacokinetics following administration of recombinant carboxypeptidase G2 in rhesus monkeys
AUTHOR(S): Adamson, Peter C.; Balis, Frank M.; McCully, Cynthia L.; Godwin, Karen S.; Poplack, David G.
CORPORATE SOURCE: Pediatr. Branch, Natl. Cancer Inst., Bethesda, MD, USA
SOURCE: Journal of Clinical Oncology (1992), 10(8), 1359-64
CODEN: JCONDN; ISSN: 0732-183X
DOCUMENT TYPE: Journal
LANGUAGE: English

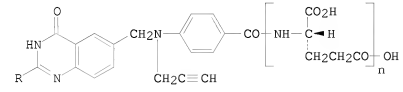
AB Rhesus monkeys were given high-dose methotrexate, followed by carboxypeptidase G2. The enzyme was capable of rapidly decreasing plasma methotrexate concns. to nontoxic levels. The administration of carboxypeptidase G2 was safe and well tolerated, and this procedure may be useful as an alternative to rescue from methotrexate toxicity by leucovorin.

OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)

L11 ANSWER 29 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1992:129559 HCAPLUS
DOCUMENT NUMBER: 116:129559

ORIGINAL REFERENCE NO.: 116:21967a,21970a
TITLE: Syntheses and thymidylate synthase inhibitory activity of the poly-γ-glutamyl conjugates of N-[5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl]-L-glutamic acid (ICI D1694) and other quinazoline antifolates
AUTHOR(S): Bisset, Graham M. F.; Pawelczak, Krzysztof; Jackman, Ann L.; Calvert, A. Hilary; Hughes, Leslie R.
CORPORATE SOURCE: Cancer Res. Campaign Lab., Inst. Cancer Res., Sutton/Surrey, SM2 5NG, UK
SOURCE: Journal of Medicinal Chemistry (1992), 35(5), 859-66
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 116:129559
GI



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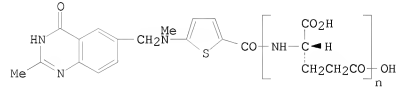
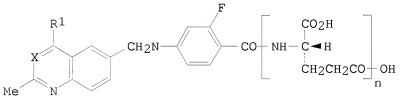


II



III

AB Title conjugates I (R = Me, n = 2, 3, 4, 5; R = H, n = 3, 4), II (n = 2, 3, 4, 5, 6) and III (X = N, R1 = OH, n = 2; X = CH, R1 = Cl, n = 3) were prepared A key step in the route involves coupling of an α-tert-butyl-protected poly-γ-glutamate of the required chain length to the appropriate 5,8-dideazapteroic acid, obtained by carboxypeptidase G2 cleavage of the parent monoglutamate, if available, or by chemical synthesis. Deprotection with trifluoroacetic acid in the final step gave the desired poly-γ-glutamyl antifolates as their trifluoroacetate salts. As inhibitors of thymidylate synthase, these polyglutamates were more potent in every case than the corresponding non-polyglutamylated drug.
OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)

L11 ANSWER 30 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1991:203058 HCAPLUS
DOCUMENT NUMBER: 114:203058

ORIGINAL REFERENCE NO.: 114:34141a,34144a
TITLE: Affinity labeling of folate transport proteins with the N-hydroxysuccinimide ester of γ-isomer of fluorescein-methotrexate
AUTHOR(S): Fan, Jianguo; Pope, Laura E.; Vitols, Karin S.; Huennekens, F. M.
CORPORATE SOURCE: Res. Inst., Scripps Clin., La Jolla, CA, 92037, USA
SOURCE: Biochemistry (1991), 30(18), 4573-80
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fluorescein-methotrexate, a derivative in which the fluorophore is linked via a diaminopentane spacer to either the α- and γ-carboxyl group of the glutamate moiety in the drug (Gapski et al., 1975), has been synthesized by an improved procedure and separated by DEAE-Trisacryl chromatog. into the α- and γ-isomers (α-F-MTX and γ-F-MTX). Each isomer was characterized by mass spectrometry, elemental anal., absorbance spectrum, TLC, and reversed-phase HPLC. Identity of the isomers was established by the following enzymic criteria: (a) γ-F-MTX (but not the α-isomer) was hydrolyzed at the pteroate-glutamate bond by carboxypeptidase G2 to yield 4-amino-4-deoxy-10-methylpteroate and γ-glutamyldiaminopentane-fluorescein; and (b) γ-F-MTX was a much better inhibitor of human dihydrofolate reductase than the α-isomer (Ki values of 0.079 and 4.6 nM). α- And γ-F-MTX were comparable as inhibitors (Ki values of 1.6 and 0.6 μM) of the transport system for reduced folates and MTX in L1210 cells, but the transporter in Lactobacillus casei was inhibited only by the γ-isomer (Ki = 4.3 μM). The γ-isomer, therefore, was selected for covalent labeling of proteins. When L. casei folate transport protein (18 kDa) was treated with γ-F-MTX that had been activated with N-hydroxysuccinimide (NHS), the protein was readily visualized as a fluorescent band on SDS-PAGE electrophoretograms. The probe was also able to detect the transporter in membranes. SDS-PAGE anal. of a Triton X 100 extract of L. casei membrane fragments that had been pretreated with activated γ-F-MTX revealed only 2 fluorescent-labeled bands, viz., the 18-kDa transporter and an unidentified 33-kDa protein. The 43-kDa transporter for reduced folate compds. and MTX in L1210 cells was also labeled by this procedure but, because of its relatively low level, visualization required immunopurifn., SDS-PAGE, and transfer to nitrocellulose, followed by immunoblotting with rabbit anti-fluorescein antibody/biotinylated goat anti-rabbit IgG/streptavidin-peroxidase conjugate. NHS-activated γ-F-MTX also facilitated visualization, via fluorescence microscopy, of folate transporters on individual L1210 cells. The validity of this procedure was demonstrated by the marked reduction in fluorescence when labeling was conducted in the presence of excess MTX or when a mutant subline (R81) down-regulated for the transporter was used. L. casei spheroplasts treated with NHS-activated γ-F-MTX were also fluorescent, and specificity was shown by reduced labeling in the presence of MTX. In this instance, however, the 33-kDa protein rather than the transporter appeared to be the labeled component.

OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

L11 ANSWER 31 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1991:484914 HCAPLUS
DOCUMENT NUMBER: 115:84914
ORIGINAL REFERENCE NO.: 115:14403a,14406a
TITLE: Rescue of experimental intrathecal methotrexate overdose with carboxypeptidase-G2
AUTHOR(S): Adamson, Peter C.; Balis, Frank M.; McCully, Cynthia

L.; Godwin, Karen S.; Bacher, John D.; Walsh, Thomas J.; Poplack, David G.

CORPORATE SOURCE: Pediatr. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA

SOURCE: Journal of Clinical Oncology (1991), 9(4), 670-4
CODEN: JCONDN; ISSN: 0732-183X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Rhesus monkey, given a neurotoxin intrathecal dose of methotrexate, survived without neurotoxicity when the treatment was followed within 5 min by administration of carboxypeptidase G2, an enzyme which hydrolyzes the drug to inactive metabolites. Pharmacokinetic studies confirmed a large decrease in cerebrospinal fluid methotrexate concns. when the drug injection was followed by administration of the enzyme.

OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

L11 ANSWER 32 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1990:604515 HCAPLUS

DOCUMENT NUMBER: 113:204515

ORIGINAL REFERENCE NO.: 113:34345a,34348a

TITLE: Occurrence and significance of diastereomers of methotrexate α-peptides

AUTHOR(S): Kuefner, Ulrike; Esswein, Angelika; Lohrmann, Ute; Montejano, Yolanda; Vitols, Karin S.; Huennekens, F. M.

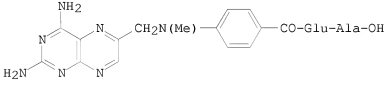
CORPORATE SOURCE: Dep. Mol. Exp. Med., Res. Inst. Scripps Clin., La Jolla, CA, 92037, USA

SOURCE: Biochemistry (1990), 29(46), 10540-5
CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



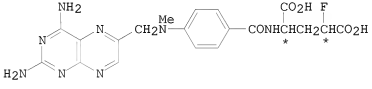
I

AB The L,L-diastereomer of methotrexate-α-alanine (L,L-MTX-Ala) (I) was synthesized by reaction of α-L-glutamyl-L-alanine di-tert-Bu ester with 4-amino-4-deoxy-10-methylpteroic acid, followed by removal of the blocking groups. It was identified by HPLC(C18 reversed-phase silica gel; acetic acid/CH3OH) as the slower of two closely spaced components in DL,L-MTX-Ala prepared previously by a different route [Kuefner et al. (1989) Biochem. 28, 2288 2297]. The L,L-diastereomer was hydrolyzed by pancreatic carboxypeptidase A (to yield MTX and Ala) twice as rapidly as the DL,L mixture Anal. of the latter by HPLC established that the slower component was hydrolyzed to MTX and that the unreactive, faster component was D,L-MTX-Ala. DL,L-MTX-Arg was resolved by HPLC (NH4OAc/CH3CN) into two closely spaced components, and the diastereomers were partially separated by chromatog. on DEAE-Trisacryl (H2O/2% NH4HCO3). Serum carboxypeptidase N hydrolyzed only the slower HPLC component (to yield MTX and Arg), thereby identifying it as the L,L diastereomer. When tested for cytotoxicity against L1210 cells, L,L-MTX-Arg (ID50 = 1.6 + 10-8 M) was more effective than the D,L diastereomer (ID50 = 2.2 + 10-7 M).

Treatment of MTX with dicyclohexylcarbodiimide and N-hydroxysuccinimide (NHS), followed by hydrolysis of the NHS ester, led to racemization in the L-glutamate moiety of MTX as shown by the fact that the product was hydrolyzed by carboxypeptidase G2 (at the pteroate-Glu bond) only to the extent of ca.50% compared to the untreated control. These observations have a broad significance, since coupling agents are employed extensively in the derivatization of MTX for attachment to affinity supports and monoclonal antibodies.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L11 ANSWER 33 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1989:587001 HCAPLUS
DOCUMENT NUMBER: 111:187001
ORIGINAL REFERENCE NO.: 111:30879a,30882a
TITLE: Biochemical and growth inhibitory effects of the erythro and threo isomers of γ-fluoromethotrexate, a methotrexate analog defective in polyglutamylation
AUTHOR(S): McGuire, John J.; Graber, Michael; Licato, Nicholas; Vincenz, Claudius; Coward, James K.; Nimec, Zenia; Galivan, John
CORPORATE SOURCE: Grace Cancer Drug Cent., Roswell Park Mem. Inst., Buffalo, NY, 14263, USA
SOURCE: Cancer Research (1989), 49(16), 4517-25
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The individual diastereomers, DL-erythro-γ-fluoromethotrexate (e-I) and DL-threo-FMTX (t-I), and their radiolabeled counterparts were prepared and characterized. Transport of e-I (Km = 9.3 μM; Vmax = 7.5 pmol/min/10^7 cells) was similar to that of methotrexate (MTX: Km = 6.6-9.9 μM; Vmax = 11.4-14.2 pmol/min/10^7 cells), while t-I (Km = 65.1 μM; Vmax = 8.4 pmol/min/10^7 cells) was transported less efficiently. Both isomers were able to saturate intracellular dihydrofolate reductase and accumulate further as unbound intracellular drug. Based on competition expts. and studies with MTX transport-defective cell lines, both isomers utilized the reduced folate/MTX transport system. Efflux half-times for the isomers were similar to those of MTX. Each isomer was equivalent to MTX in its ability to inhibit dihydrofolate reductase activity and bind to intracellular dihydrofolate reductase when the intracellular drug concentration was limiting. Both isomers had drastically diminished capacity to be metabolized to poly(γ-glutamyl) metabolites by isolated folylpolyglutamate synthetase and in whole cells; t-I was metabolized to a slightly lesser extent than e-I. Using the CCRF-CEM human leukemia and H35 rat hepatoma cell lines, the growth-inhibitory effects of e-I were almost the same as those of MTX during continuous exposure, while t-I was slightly less potent. This difference in growth-inhibitory potency of the 2 isomers correlated with their ability to inhibit de novo thymidylate synthesis in the H35 cell line. Both diastereomers of I are similar in

their properties to MTX, except that both are incapable of being readily converted to polyglutamate derivs. As a result of these properties, both isomers could be used under appropriate conditions in comparative studies with MTX to define the roles of MTX polyglutamates.

OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

L11 ANSWER 34 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1989:526607 HCAPLUS
DOCUMENT NUMBER: 111:126607
ORIGINAL REFERENCE NO.: 111:21003a,21006a
TITLE: Carboxypeptidase G2 enhances trimetrexate cytotoxicity in CCRF-CEM cell lines sensitive and resistant to methotrexate
AUTHOR(S): Romanini, A.; Chou, T. C.; Bertino, Joseph R.
CORPORATE SOURCE: Program Dev. Ther. Clin. Invest., Mem. Sloan-Kettering Cancer Cent., New York, NY, 10021, USA
SOURCE: Advances in Enzyme Regulation (1989), 28, 323-33
CODEN: AEZRA2; ISSN: 0065-2571
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Carboxypeptidase G2 (CPG2), an enzyme produced by Pseudomonas strain RS-16, degrades folates as well as methotrexate and other folic acid analogs such as aminopterin and dichloromethotrexate, but not the non-classical folate antagonist trimetrexate (TMTX). The possibility of enhancing TMTX cytotoxicity of CPG2-induced depletion of intracellular folates was investigated in human leukemic CCRF-CEM cells and in three methotrexate resistant sublines of these cells with different mechanisms of resistance, CCRF-CEM/E, a subline with increased DHFR; CCRF-CEM/P, a subline defective in polyglutamylation and CCRF-CEM/T, a subline with impaired MTX uptake. The cytotoxic effect was detected using a colorimetric assay with the stain MTT. Dose-effect relationships of single drugs alone and in combination were analyzed by the median-effect principle and by the combination indexes for the quantitation of synergism or antagonism with the aid of a microcomputer. TMTX alone was very effective on the parent and all the resistant cell lines (CCRF-CEM/E, CCRF-CEM/P, CCRF-CEM/T) with ED50 values in the nanomolar range (1.4, 1.6, 1.5 and 0.7 nM, resp.) following 5 days of exposure. The ED50s of CPG2 for these cell lines were 3.5, 2.6, 26.6, and 7.9 + 10-5 U/mL, resp. A synergistic cytotoxic effect of TMTX after simultaneous continuous exposure was observed with CPG2 on CCRF-CEM cells and on the three resistant cell lines.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L11 ANSWER 35 OF 35 HCAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1985:200035 HCAPLUS
DOCUMENT NUMBER: 102:200035
ORIGINAL REFERENCE NO.: 102:31295a,31298a
TITLE: Purification and properties of carboxypeptidase G2 from Pseudomonas sp. strain RS-16. Use of a novel triazine dye affinity method
AUTHOR(S): Sherwood, Roger F.; Melton, Roger G.; Hughes, Peter
CORPORATE SOURCE: Microb. Technol. Lab., Public Health Lab. Serv. Cent. Appl. Microbiol. Res., Porton Down/Salisbury, SP4 0JG, UK
SOURCE: European Journal of Biochemistry (1985), 148(3), 447-53
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English

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AB   A folate-degrading enzyme, carboxypeptidase G2 (I) was
     purified on a large scale from Pseudomonas species strain RS-16.
     Homogeneous I was obtained by a 3-step procedure involving ion-exchange
     chromatog. and a novel triazine dye (affinity) chromatog. step which
     utilizes Zn2+ to promote adsorption of I.  I was selectively eluted by the
     use of EDTA and a step change in pH.  I was a dimeric protein (mol. weight =
     83,000) with 2 identical subunits of 41,800 and contains 4 atoms of
     Zn/enzyme mol., which were required for full activity, followed
     Michaelis-Menten kinetics with Km values of 4.0 μM for folate, 8.0
     μM for methotrexate, and 34.0 μM for 5-methyltetrahydrofolate, the
     predominant form of reduced folate found in plasma.
OS.CITING REF COUNT:     79     THERE ARE 79 CAPLUS RECORDS THAT CITE THIS
                                RECORD (79 CITINGS)


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     (FILE 'HOME' ENTERED AT 12:39:43 ON 28 JUN 2010)

     FILE 'REGISTRY' ENTERED AT 12:39:57 ON 28 JUN 2010
L1           44 S CARBOXYPEPTIDASE G2
L2          120 S METHOTREXATE
L3            1 S RALTITREXED
L4            1 S AG 2037
L5            1 S LY 309887

     FILE 'CAPLUS' ENTERED AT 12:40:57 ON 28 JUN 2010
L6           29 S L1
L7            0 S L6 AND (L2 OR L3 OR L4 OR L5)
              E US2007-590789/AP
L8            1 S E3

     FILE 'ZCAPLUS' ENTERED AT 12:42:48 ON 28 JUN 2010
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                E CARBOXYPEPTIDASE G/CT
                E CARBOXYPEPTIDASE G2/CT
                E E3+ALL
                E E27+ALL

     FILE 'HCAPLUS' ENTERED AT 12:44:26 ON 28 JUN 2010
L9          224 S CARBOXYPEPTIDASE G2
L10          35 S L9 AND (L2 OR L3 OR L4 OR L5)
L11          35 DUP REM L10 (0 DUPLICATES REMOVED)

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   163.79     214.70

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
```

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STN INTERNATIONAL LOGOFF AT 12:55:48 ON 28 JUN 2010